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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/570,122	02/28/2006	Christine Power	ARS.122	7430

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SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER	
DEBERRY, REGINA M	
ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
08/06/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/570,122	POWER ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-50,55 and 57-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-50,55 and 57-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 23 June 2010 has been entered.

Status of Application, Amendments and/or Claims

The amendment and Applicant's arguments, filed 23 June 2010, have been entered in full. Claims 1-45, 51-54, 56 are canceled. Claims 46 and 66 are amended. New claims 67-86 are added. Claims 46-50, 55, 57-86 are under examination.

Claim Rejections-35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 71 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 71 incorrectly depends from claim 67. Claim 71 should depend from claim 70.

Claim Rejections-35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46-50, 55, 57-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for treating a fibrotic disease comprising administering to a patient having a fibrotic disease a therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier and a polypeptide comprising **SEQ ID NO:2**, wherein said fibrotic disease is lung fibrosis or liver fibrosis

does not reasonably provide enablement for:

a method for treating a fibrotic disease comprising administering to a patient having a fibrotic disease a therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier and a polypeptide comprising **SEQ ID NO:5 or SEQ ID NO:7**, wherein said fibrotic disease is lung fibrosis or liver fibrosis.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification states that the present invention is in the field of fibrotic diseases/connective tissue disorders and the use of INSP035 for the treatment and/or prevention of fibrotic diseases. Combination of INSP035 with an interferon, a TNF antagonist or a further anti-fibrotic agent such as OPG is also within the present

invention (page 1, lines 3-10). The specification teaches the full length cDNA of human INSP035 as SEQ ID NO:1 and the corresponding amino acid sequence as SEQ ID NO:2 (page 9, lines 23-26). The sequence listing teaches SEQ ID NO:2 as having 163 amino acids. The specification teaches that the cDNA of human INSP035 starting at the 2nd methionine (called INSP035 medium form) from INSP035 has been cloned. The cDNA is SEQ ID NO:4 and the corresponding amino acid sequence is SEQ ID NO:5 (page 9, lines 26-29). The sequence listing teaches SEQ ID NO:5 as having 88 amino acid residues. The specification teaches that a modified INSP035 medium form with an isoleucine substitution at position 1 has been generated as SEQ ID NO:7 (page 9, lines 29-31). The sequence listing teaches SEQ ID NO:7 as having 88 amino acid residues. The specification states that the invention is based on the finding that INSP035 is a potent inhibitor of TRAIL in an *in vitro* assay designed to select anti-apoptic molecules in fibroblasts with osteoprotegerin (OPG) as control. The specification states that like OPG, INSP035 is able to counteract the apoptotic effect of soluble human recombinant TRAIL on fibroblast, thereby consistently reducing fibroblasts' apoptosis (page 7, lines 1-6). The specification states that administered OPG resulted in significant amelioration of fibrosis in an established animal model of lung fibrosis. The specification states that on the basis that OPG and INSP035 share common functionalities and on the findings that TRAIL stimulates collagen production, INSP035 is suggested to be useful in the treatment of fibrosis. The specification proposes that INSP035, as a TRAIL inhibitor, might lower the amount of TGFbeta present in the cells, which in turn would reduce

collagen synthesis known to be deleterious in the pathogenesis of fibrosis (page 8, lines 9-18).

The specification teaches that INSP035 and its variants are potent inhibitors of TRAIL in an *in vitro* assay designed to select anti-apoptotic molecules (Figures 1-3; page 7, lines 16-34 page 25, lines 22-31 and page 27, lines 4-16). Applicant argues in the response (filed 23 June 2010) that the poly-histidine tagged forms of the additionally claimed polypeptides exhibited similar activity to the allowed peptide. Applicant cites page 7, lines 16-34; Figure 1 and page 8.

The instant claims are not enabled for the full scope because the specification fails to teach how to treat a fibrotic disease *in vivo* using fragments and/or mutants of full length INSP035 (SEQ ID NO:2). SEQ ID NO:5 and SEQ ID NO:7 comprise 1/2 the amount of amino acid residues as SEQ ID NO:2. Further, SEQ ID NO:7 comprises a mutation. The disclosure provides no guidance as to which regions of the INSP035 protein would be tolerant of modification and which would not, and it provides no working example of any variant sequence which would be within the scope of claims (i.e. an actual *in vivo* treatment employing SEQ ID NO:5 and SEQ ID NO:7). Applicant argues that the additionally claimed polypeptides exhibited similar activity to the allowed peptide. This is not found persuasive because it is extremely complex to predict protein structure from sequence data and in turn utilizing calculated structural determinations to ascertain functional aspects of the protein. It is in no way predictable that randomly selected mutations, deletions, etc. in the disclosed sequence would afford a protein having activity comparable to the one disclosed. For example, the specification states

that INSP035 was identified as a leptin (page 5, lines 10-21), but Figure 2 demonstrates that leptin *did not* affect TRAIL-mediated apoptosis, like INSP035 in the *in vitro* assay. Further, just because a variant protein has activity in an *in vitro* assay does not necessarily mean that variant will have the same activity *in vivo*. For example, Murrills et al. (Bones 35:1263-1272, 2004) teach the PTH protein as an injectable treatment for osteoporosis. Murrills et al. teach a deleted form of PTH called MPTH, wherein the carboxy amino acids are deleted. The MPTH mutant demonstrated receptor binding, cAMP activity, intracellular calcium signaling and CRE-luciferase expression in the *in vitro* assays (page 1267; Figures 1-3). *However*, the MPTH mutant was completed inactive when administered to ovariectomized rats (page 1267, last paragraph-page 1268). Twining et al. (The Journal of Biological Chemistry, 276/25:23135-23143, 2001) teach that a mutation of a lysine to a glutamine in Tn5 transposase resulted in full activity in an *in vitro* assay, but was only 1% as active as the wildtype *in vivo*. Twining et al. state that there are steps that may be affected by the mutation *in vivo* but are not tested *in vitro*. These include *in vivo* stability and binding accessory molecules, which are not required *in vitro* (abstract; page 23142, last paragraph-23143). Thus, it could not be predicted that the cell culture data, which employed fragments and/or mutants of full length INSP035 would be correlative/effective with therapeutic agents for *in vivo* treatment of fibrotic diseases.

Due to the large quantity of experimentation necessary to discern which structural features in the INSP035 protein would be tolerant of modification and which would not in order to provide anti-fibrotic activity *in vivo*, the lack of direction/guidance

presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention and the state of the prior art which establishes that there are activity differences between variant proteins evaluated *in vitro* versus *in vivo*, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/R. M. D./
Examiner, Art Unit 1647
7/29/10
/Marianne P. Allen/
Primary Examiner, Art Unit 1647